OTSUKA AMERICA PHARMACEUTICAL, INC.

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October 3, 2000

Dockets Management Branch (HFA-305)
Food and drug Administration
5630 Fishers lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 00D–1418

Dear Sirs:

Please find attached comments from Otsuka America Pharmaceutical Inc. (OAPI) on the International Conference on Harmonisation: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, ICH Q7A, Step 2 document.

Please feel free to contact me at (301) 527-4701 should you need additional information or clarification.

Sincerely yours,

Suva B. Roy

Suva B. Roy, Ph.D.
Senior Director, Regulatory Affairs CMC

00D-1418 C6

Otsuka America Pharmaceutical Company Comments on International Conference on Harmonisation: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, ICH Q7A, Step 2, Document

General Comments

The definition of Active Pharmaceutical Ingredient appears to be identical to drug substance, a term used in all other ICH guidances. In order to maintain consistency we suggest that the same terminology be used in all ICH guidances.

It appears that "In-process Control" or "Process Control" tests can be performed by either the Quality Unit or the Manufacturing Unit. This can be cause for confusion. In order to maintain clarity of missions between the Quality and Manufacturing Units it may be advisable to refer to the tests by different names. Perhaps, tests performed by the Quality Unit may be called "In-process Control" and the those performed by the manufacturing Unit as "In-process Check".

Specific Comments

Lines 58-59 - States "API Starting Materials normally have defined chemical properties and structure". It is unclear what is meant by defined chemical properties, examples may help adding to the clarity.

Line 131 - We suggest including a definition for "Master production instructions" in the glossary. It appears to be synonymous with Master Production Control records in 21CFR 211.186.

Lines 198-199 - The requirement that responsibilities of ALL personnel engaged in the manufacture of intermediates and API is overly burdensome. We recommend that the sentence be rephrased as "The responsibilities of *key* personnel engaged in the manufacture of intermediates and APIs should be specified in writing."

Lines 384-385 - We recommend that the sentence be rephrased as " Establishing the maximum time that may elapse between completion of processing and equipment cleaning or between equipment cleaning and subsequent reuse when appropriate."

Lines 394-395 - We suggest that logs should also be maintained of the use and cleaning of non-dedicated equipment. This should of course exclude utensils like scoops, spatulas etc.

Lines 461-464 - Often when an API reaches the retest date, it is tested and completely used up within a short period after the test. It may be more appropriate to require that the records be retained for a specific period time after the last retest date. We recommend the following sentence instead "For APIs with retest dates, records should be retained for 2 years after the last retest date."

Lines 518-521 - The requirement that the second person checking the master production instructions should also be from the Quality Units is too restrictive. Also, an experienced production person may be better suited to perform this function. We recommend the following sentence instead "To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person in the Quality Unit and independently checked, dated and signed by a qualified second person. The second person may from the Quality Unit, or the Production Unit."

Lines 675-676 - In order to assure reproducibility of batch to batch quality, it is prudent to test three randomly batches whenever possible. We recommend the sentence be rephrased as "Full analysis should be conducted on at least three randomly selected batches, whenever possible, before reducing in-house testing."

Lines 771-773 - In-process controls are generally performed at critical stages of manufacture. The use of the word Critical in the sentence is redundant. We recommend that it be deleted.

Lines 893-894 - We recommend replacing "may" with "should" in this sentence. The revised sentence to read "This examination should be part of the packaging procedure."

Lines 946-949 - We recommend replacing "may need" in the sentence with "should" in this sentence. The revised sentence to read "If the API needs to of a specified microbial purity, appropriate action limits for total microbial counts, objectionable organisms, and endotoxins should be established and met."

Lines 1064-1069 - Similar to records retention schedule on lines 461-464 we recommend that the sample retention should also be linked to the last retest date. We recommend the following sentence instead "For APIs with retest dates, samples should be retained for 2 years after the last retest date."

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